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Sex Hormone Influences on Cardiovascular Risk

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centage of patients with sustained castrate levels of testosterone and similar metastasis-free survival in the two groups. Benefits of tE2 as compared with LHRH agonists include improved bone health (lower incidence of fractures), a better metabolic profile (glucose and lipids), and higher overall quality-of-life scores attributed to fewer hot flashes, better sleep patterns, and less fatigue.¹

As Sears and Schuller note, gynecomastia is a side effect of estradiol administration and an important consideration for some patients who are considering options for androgen-deprivation therapy. The data that they describe about breast size and extent of gynecomastia with estradiol in persons assigned male sex at birth is an important addition to the conversation around choices for androgen-deprivation therapy. Their highlighting of how gynecomastia can be discussed with patients is a valuable addition to our article.

Grossmann and Russell discuss the use of lower-dose tE2 administered as a gel in addition to LHRH agonist injections as another strategy for androgen-deprivation therapy. Their randomized trial involving 78 men showed a lower daily frequency of hot flashes with an LHRH agonist plus estradiol gel than with an LHRH agonist plus placebo but did not show a better overall quality of life,² and they reflect that higher estradiol doses may have been more effective. The add-back approach increases polypharmacy and potentially costs, and data derived directly from patients indicates a strong preference for avoiding injections.³ Longer-term follow-up of patients who were recruited through the STAMPEDE-1 and PATCH trial networks will continue with the use of electronic health records.

A recent survey of more than 800 men with prostate cancer shows the importance of fully discussing the immediate and longer-term effects of starting androgen-deprivation therapy.⁴ In our trial, 85% of the patients who received tE2 reported any gynecomastia (events of grade ≥ 2 occurred in 37%), as compared with 42% who received LHRH agonists (events of grade ≥ 2 occurred in 9%); however, hot flashes were reported by 44% of the patients who received tE2 (events of grade ≥ 2 occurred in 8%), as compared with 89% who received LHRH agonists (events of grade ≥ 2 occurred in 37%). The survey also shows the interest from patients for different forms of androgen-deprivation therapy, including tE2.

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Since publication of the article, the authors report no further potential conflict of interest.

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Sex Hormone Influences on Cardiovascular Risk

TO THE EDITOR: In their review article (April 16 issue),¹ Skeith and Bates provide an important review of cardiovascular risk with hormonal contraception and menopause treatment. However, when discussing combined hormonal contraceptives, the authors do not differentiate between products containing ethinylestradiol (EE) and those containing natural estrogens such as estradiol (E2) and estetrol (E4). The evidence for less

thrombosis risk with natural estrogens than with EE products is consistent across similar levels.

First, randomized hemostasis studies have shown that natural estrogens induce substantially less acquired activated protein C (APC) resistance than EE-containing drugs.² The results of a validated endogenous thrombin potential–based normalized APC sensitivity ratio assay predicted relative venous thromboembolism risks of 1.50 with

E2–norgestrel acetate and 1.45 with E4–drospirenone, as compared with 2.42 with EE–levonorgestrel and 3.43 with EE–drospirenone.³ Second, meta-analysis of population-level data showed a hazard ratio of 1.95 for EE–levonorgestrel as compared with E2-based drugs.³ Third, analyses of pharmacovigilance disproportionality from Europe and the United States both showed statistically lower thrombotic-event reporting ratios for E2- and E4-containing products — more than 50% below the signal for the EE-based drugs.^{4,5} Together, these data support the importance of risk stratification in making decisions regarding estrogen content for combined hormonal contraception.

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Jonathan Douxflis reports having received lecture fees from Daiichi Sankyo, Diagnostica Stago, Portola, Roche, and Roche Diagnostics and lecture and consulting fees from Estetra and Gedeon Richter. Mitchell D. Creinin reports having received speaking honoraria from Mayne, having stock options with Femasys, and receiving consulting fees from Bayer, Estetra SRL, Gedeon Richter, Mayne, Medicines360, and Merck Sharpe Dohme. The authors report that the Department of Obstetrics and Gynecology, University of California, Davis, receives contraceptive research funding for Mitchell D. Creinin from Femasys, Medicines360, Merck, Sebela, and Myovant (Sumitomo Pharma). Jean-Michel Foidart reports having been a board member for Mithra. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In their review article on the risk of cardiovascular events associated with sex hormone therapy, the authors acknowledge that the risk of venous thromboembolism (VTE) during testosterone supplementation remains poorly understood and that some studies have shown an increased risk, particularly during the first 6 months of treatment. We were therefore surprised that the accompanying Key Points box states that testosterone replacement does not increase the risk of VTE.

In the randomized TRAVERSE trial,¹ testosterone-replacement therapy was associated with an increased incidence of acute pulmonary embolism in men with hypogonadism. Testosterone also increases hemoglobin and hematocrit levels, which are both associated with VTE in epidemiologic cohorts.² In a recent analysis of the TriNetX Research Collaborative Network, we observed a higher risk of VTE events in 117,908 men with hypogonadism who received testosterone than in matched untreated controls (hazard ratio, 1.26; 95% confidence interval [CI], 1.18 to 1.34; $P < 0.001$).³ Taken together, these converging data suggest that the assumption of no increased VTE risk with testosterone supplementation may be overstated.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: We acknowledge the important work that Douxflis and others have undertaken to examine the effects of natural estrogens on the hemostatic system and the risk of VTE. Although the systematic review and meta-analysis that is referenced showed a significantly lower VTE risk with estradiol-based combined oral contraceptives than with those containing

synthetic estrogens (odds ratio, 0.67; 95% CI, 0.51 to 0.87),¹ the odds ratio for the comparison with the combined oral contraceptive that is viewed as safest (ethinyl estradiol and levonorgestrel) was not significantly different at 0.80 (95% CI, 0.54 to 1.17). Even with adjustments, the upper boundary of the 95% confidence interval fell below 1.0 for estradiol dienogest (hazard ratio, 0.49; 95% CI, 0.29 to 0.85) but not for norgestrel acetate–estradiol (hazard ratio 0.68; 95% CI, 0.37 to 1.25).

Although an analysis of pharmacovigilance data can identify drug-related safety signals or provide reassurance about safety, it is hampered by issues of data quality and consistency, reporting bias, confounding, and inability to prove causality. Consequently, results are generally not accepted as definitive. Of note, the American pharmacovigilance data² that corroborate the corresponding data from Europe³ only became available online after our article was accepted for publication. We recognize the growing information about natural estrogen contraceptives and look forward to incorporating these accruing data into future guidelines and recommendations.

Some caution is suggested in the interpretation of data surrounding the risk of pulmonary embolism with testosterone therapy in the TRAVERSE trial.⁴ This finding was a component of a tertiary outcome, and the diagnosis was made in 24 of 2596 patients (0.9%) in the testosterone group and in 12 of 2606 patients (0.5%) of those in the placebo group. In addition, the investigators appropriately had made no prespecified plan to analyze this outcome.

We congratulate Bonnet and colleagues on their TriNetX Research Collaborative Network

publication. Like all observational datasets, this one has limitations that prevent conclusions about causality. Therefore, with the caveats contained in the body of our article, no conclusive data at this point show that testosterone is associated with an increased risk of VTE.

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Since publication of the article, the authors report no further potential conflict of interest.

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